REMARKS

1. Written Description Issues (OA §6)

Claims 1, 15-18, 31 and 32 have been rejected for alleged lack of written description. We traverse.

The examiner states at the top of page 10 of the office action:

> Applicant has amended claim 1 to recite "...dissolving parental immunoglobulins....under conditions resulting in synthetic glycosylation of said parental immunoglobulins, and wherein said antimicrobial composition has increased bactericidal activity at least in part as a result of said synthetic glycosylation"; claim 15 to recite "....Activity relative to said parental immunoglobulins"; claims 16-18 and 32 to recite "parental immunoglobulins"; claim 31 to recite "...native naturally glycosylated immunoglobulins, native deglycosylated immunoglobulins, recombinant deglycosylated immunoglobulins and recombinant unglycosylated immunoglobulins". These phrases do not appear in the specification, or original claims as filed. Applicant does not point out specific basis for this limitation in the application, and none is apparent.
>
> To overcome this rejection Applicant must specifically point out the support for this limitation or cancel the new matter from the claims.

The claimed composition comprises lysozyme and synthetically glycosylated immunoglobulin. Basis for synthetic glycosylation appears at P9, L19-28:

> It is preferred that the used immunoglobulins remain functional for a prolonged time, also after administration. Thus, it is preferred that the immunoglobulins are intact and resistant towards bacterial proteases. This is achieved by glycosylating immunoglobulins, for example by glycosylating the FC fragment of the immunoglobulins. An example is wherein 10 g pooled immunoglobulins 77,0% IgG, 7,6% IgA and

> 15,4% IgM are dissolved in 25 ml 1M solution of glucose and incubated at 45°C. During the incubation the glucose will establish covalent bonds particularly to the Fc fragment of the IgG molecule which can be tested by demonstrating the loss of ability to bind complement. However, the ability of the glycosylated immunoglobulins to agglutinate is unchanged.

This is clearly a synthetic (in vitro) glycosylation (as distinct from natural glycosylation, in vivo), as it is achieved by dissolving immunoglobulins in a glucose solution. Indeed, P9, L14-15 states "glycosylated immunoglobulins are synthesized chemically".

Further basis for synthetic glycosylation appears at P21, L32-P22, L2:

> The glycosylation of the immunoglobulins may be carried out in any suitable manner. In one embodiment the immunoglobulins are dissolved in a solution comprising the disaccharide or monosaccharide in question. In a preferred embodiment the immunoglobulins are dissolved in a glucose solution and incubated for a predetermined period of time to allow the immunoglobulins to be glycosylated. Examples of other monosaccharides and disaccharides are discussed above.

Thus, there is clear "written description" for "synthetically glycosylated".

The term "parental immunoglobulins" is strictly a term of convenience. We needed to have, for clarity of comparative functional limitations, a way of referring to the immunoglobulins as they existed prior to said synthetic glycosylation.

Plainly, if there is "possession" of synthetic glycosylation of an immunoglobulin, there must be "possession" of the starting immunoglobulin, whether it be called a "parental" immunoglobulin, a "first" immunoglobulin, an "initial" immunoglobulin, a "starting" immunoglobulin, or

something else.

The term "native immunoglobulin" is used on page 4, lines 5 and 13 (in the prior art context, "repeated experiments in vitro has shown lack of effect on Gram negative bacteria using the combination of lysozyme and **native** immunoglobulins") and the term "native antibodies" on page 23, lines 19 and 32. The latter were clearly contrasted with "glycosylated antibodies" at P23, L25 and P24, L3.

We would simply replace "parental" immunoglobulin with "native" immunoglobulin save for the fact that it is clearly contemplated that the "glycosylated immunoglobulins can be derived "as a result of genetic engineering as recombinant proteins". See P9, L13-14. If so, then this would imply glycosylation of a recombinant immunoglobulin rather than a native immunoglobulin.

We have amended claims 1, 16-18, 31 and 32 to recite "non-synthetically glycosylated" in place of "parental".

With respect to the "increased bactericidal activity at least in part as a result of said synthetic glycosylation", that is based on comparison of experiment 1c with 1b, and of 2b with 2a. See also P4, L2-13.

Finally, we have amended claim 31 to provide that the non-synthetically glycosylated immunoglobulin is a native immunoglobulin, with basis as previously stated.

2. Prior Art Issues (OA §5)

Amended claim 1 as introduced under the previous Office action is directed towards an antimicrobial composition comprising synthetically glycosylated immunoglobulins directed towards antigens present on the surface of Gram negative bacteria. With respect to affinity towards Gram negative bacteria, the Examiner draws attention to Stephan et al., column 2, lines 35-44, wherein it is disclosed that the immunoglobulins of Stephan et al. have effect on mice infected with the Gram negative bacteria Ps. Aeruginosa. Stephan et

al. disclose that infected mice treated with a mixture of immunoglobins and the tetrapeptide Tuftsin resulted in survival of 67% of the infected mice, while only 44% of the mice treated with native immunoglobulins survived. In Example 1 and 2 of the present application it is disclosed that bacterial exposure of the antimicrobial composition of the present invention results in 100% kill of the Gram negative as well as Gram positive bacteria. This further adds to the argumentation that the synthetically glycosylated immunoglobulins of the present invention are both different from, and has improved properties over the immunoglobulins of Stephan et al.

The Examiner further states that absent evidence to the contrary, the immunoglobulins of Stephan et al. are necessarily directed towards antigens on the surface of Gram negative bacteria. We disagree with the Examiner.

Stephan et al. disclose in column 4, lines 5-15 that the immunoglobulins are able to capture fragments of the bacteria as a result of a preceding lysis of the bacteria by lysozyme, which are hereby supplied to the elimination process by immune cells. That the immunoglobulins are able to capture only fragments of the bacteria does not imply that the immunoglobulins bind to bacterial surface antigens. On the contrary, it seems likely that the immunoglobulins of Stephan et al. bind to intracellular antigens. Thus, the invention of Stephan et al. is directed towards remnants of bacteria that are already lysed.

In contrast hereto, the synthetically glycosylated immunoglobulins of the present invention recognize antigens present on the surface of the Gram negative bacteria. This is an important aspect of the present invention since it is the binding of the synthetically glycosylated immunoglobulins to antigens present on the cell wall of the bacteria that induces an alteration of the surface of the lipopolysaccharide layer, and hereby enable lysozyme to attack and degrade the

underlying peptidoglycan layer, ultimately resulting in bacteriolysis. This is described on page 4, lines 30-34 and on Fig. 5 of the present application. Thus, the present invention are directed towards intact pathogenic bacteria, and the synthetically glycosylated immunoglobulins are directly involved in the lysis process of the Gram negative bacteria.

We therefore maintain that the antimicrobial composition comprising lysozyme and synthetically glycosylated immunoglobins directed towards antigens present on the surface of Gram negative bacteria of the present invention, is both novel and non-obvious over the invention of Stephan et al.

Combining Stephan et al. with Shu et al. will still not enable the skilled person to arrive at the subject matter of the present invention. The conjugation of the lysozyme of Shu et al. with polysaccharides serves the purpose of increasing the emulsifying properties of lysozyme compared to other known emulsifiers. As described in detail below the synthetic glycosylation of the immunoglobulins of the present invention serves a very different purpose, and it is the properties owing to the synthetically glycosylated immunoglobulins that distinguish the antimicrobial composition of the present invention from prior art.

As a direct result of the synthetic glycosylation, the immunoglobulins of the present invention have improved properties towards degradation by proteases, and thus have increased half-lives. It is well known that bacteria are equipped with proteolytic enzymes, and therefore it is a great advantage that the synthetically glycosylated immunoglobulins of the present invention are able to resist hydrolytic attack from proteases in a timeframe long enough for the synthetically glycosylated immunoglobulins to bind to antigens on the surface of the bacteria, induce alterations in the lipopolysaccharide layer of the bacteria and thereby pave the way for the bacteriolytic action of lysozyme.

Contemplating the prior art that teaches that

polysaccharide conjugated lysozyme is an excellent emulsifier (Shu et al.) would not lead the skilled person to conclude that native immunoglobulins (Stephan et al.) could be improved by synthetic glycosylation and thereby obtain increased properties towards lysis of Gram negative bacteria.

Respectfully submitted,

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